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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,016	08/30/2001	Carlos Martinez Alonso	46309-253995	8132

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EXAMINER	
YAEN, CHRISTOPHER H	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,016	ALONSO ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-61* is/are pending in the application.

4a) Of the above claim(s) *31-36,41-57,59 and 60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-39,58 and 61* is/are rejected.

7)☒ Claim(s) *40* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/12/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence alignment (3 pages)*.

DETAILED ACTION

Re: Alonso *et al*
Priority Date: 10 September 1998

Election/Restrictions

1. Applicant's election with traverse of group II (claims 37-40, 58, and 61) in Paper No. 03032004 is acknowledged. The traversal is on the ground(s) that the lack of unity is improper because Nagase *et al* disclose hundreds of cDNA clones of which are not functionally related. Applicant further argues that there is no therapeutic function of the specific cDNA clone (see page 9), and that the DIO-1 nucleic acid sufficiently links the claimed inventions. This is not found persuasive because the invention is drawn to the product *per se* and the functional aspects or intended use does not breath any patentable weight in determining whether the product is different from that disclosed by Nagase *et al*. Moreover, the technical feature linking the different groups appears to be a sequence of SEQ ID No: 1 or variants thereof. Because Nagase *et al* taught a sequence which is a "variant" of SEQ ID No: 1, the instant invention does not seem to provide a contribution over the prior art. Therefore, the unity of the invention cannot be held and the separation of the groups are deemed proper.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 31-61 are pending, claims 31-36, 41-57, and 59-60 are withdrawn from further consideration as being drawn to a non-elected invention.

3. Claims 37-40, 58 and 61 are examined on the merits.

Information Disclosure Statement

4. The Information Disclosure Statement filed 3/12/2001 is acknowledged and considered. A signed copy of the IDS is attached hereto.

Specification

5. The disclosure is objected to because of the following informalities: The specification objected to on page 3, line 20, and page 4, line 28 for improper disclosure of amino acid sequences without a respective sequence identifier, i.e. a SEQ ID Nos:. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d). ***Failure to supply the appropriate sequences identification numbers in response to this action will be considered non-responsive.***

Appropriate correction is required.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claim 61 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 61, as written, do not sufficiently distinguish over proteins as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

Claim Rejections - 35 USC § 112, 2nd paragraph

8. Claim 61 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claim 61, in the recitation of the term "compound", it is vague and indefinite because a compound is defined as having more than one element of which has not been specifically named or claimed.

Claim Rejections - 35 USC § 112, 1st paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 37-39, 58, and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case has only set forth an amino acid sequence of SEQ ID No: 2 or 4 and therefore the written description in this case is not commensurate in scope to claims that read on variants or alleles thereof, nor is there written description for agonists or antagonists of of SEQ ID No: 2 or 4.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

What are allelic variants? Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not

defined, nor in this case, is the structure of allelic variant proteins encoded by allelic variant genes defined. With the exception of SEQ ID Nos:2 and 4, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides, polypeptides, or variants thereof , therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Furthermore, although drawn specifically drawn to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or

physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for allelic variants is provided in the specification on page 2 line 12-13 where it is disclosed that " 'variants' and 'alleles' mean that they are derived from the sequence given in the figures and have the same function". However, no disclosure, beyond the mere mention of variants or alleles is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

The claims also recite "agonists" or "antagonist" to SEQ ID No: 2 or 4 as part of the invention. However, there does not appear to be an adequate written description in the specification as-filed of the essential structural feature that provides the recited function of antagonizing the polypeptides or SEQ ID No: 2 or 4. The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Applicant does not appear to have reduced to practice any agonists or antagonists of either SEQ ID No: 2 or 4. Neither has Applicant provided a sufficient written description of any structure that may be correlated with the desired agonistic or antagonistic function. An agonist or antagonist encompasses *any* molecule with the functional activity of enhancing or inhibiting death-promoting activity. Thus the genus of compounds encompassed by this term is extensive and the artisan would not be able to recognize that Applicant was in possession of the invention as now claimed.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

Therefore only an isolated polypeptide of SEQ ID No: 2 or 4 meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 112, 1st paragraph

11. Claims 58 and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or

lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The claims are drawn to a pharmaceutical composition comprising compounds of SEQ ID No: 2 or 4 and one or more excipients or a compound for use as a medicament comprising the polypeptides of SEQ ID No: 2 or 4. The specification has taught the induction of apoptosis leads to the up-regulation of the DIO-1 gene upon IL-17 starvation of WOL-1 cells. The specification has taught that the transient transfection of the DIO-1 gene into BAF/3 cells leads to cell death via apoptosis. The specification has also taught that the DIO-1 gene is involved in limb formation, and when administered via retroviral vector that the gene can cause the failure of limb formation *in vivo*. However, the specification has failed to provided one of skill in the art with any reasonable guidance with regard to making or using a pharmaceutical compound comprising the polypeptides of SEQ ID No: 2 or 4 with any *in vivo* predictability.

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is

well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "Petri-dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from

those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Mak et al. (Nat. Rev. Immunol. 2001; 1:11-19) review that although gene-targeting has provided great insights into gene function, there are caveats that must be considered when assessing the phenotypes of genetically engineered mice (see entire reference, but especially the bridging paragraph of pages 13 and 14). In particular, Mak et al. note that engineered mutations in one gene can affect the expression of unaltered neighboring genes, giving rise to phenotypes that are unconnected to the gene of interest; and that gene deletions can also affect the architecture of an organ, such as the lymph nodes or spleen, which would have secondary effects on cells within these organs. Mak et al. conclude that there is a danger that such effects might be misinterpreted as primary effects of the gene mutation on the cells themselves.

Chang H *et al* (Mol. Cell. Endocrinol.) (Ireland) 2001; 180(1-2):39-46) disclose a knockout of a component of the TGF-β signal transduction cascade, and conclude that "the expression pattern of a component in a TGF-superfamily signal transduction cascade does not necessarily predict its in vivo function" (see abstract).

Thus although the specification discloses that a genetic inactivation of DIO-1 via retroviral vector in chick embryos for the inactivation of limb development; it is unpredictable if these phenotypes are due directly to inactivation of DIO-1. Consequently, it would require undue experimentation of the skilled artisan to establish that the phenotype observed in the DIO-1 inactivated chick embryos was a direct consequence of inactivation of the gene encoding DIO-1 or if such effects are directly

correlative to its actual in vivo function. Therefore, in the absence of such objective evidence the application of DIO-1 polypeptides of SEQ ID No: 2 or 4 as a pharmaceutical composition in the instantly claimed invention would be highly unpredictable. The skilled artisan cannot predict with any certainty that the polypeptides claimed would function in a manner similar to that exemplified by the DIO-1 retroviral chick embryo model. As a result the skilled artisan would be forced into undue experimentation to practice the instant invention commensurate in scope to the claims.

Therefore, given the lack of guidance with regard to the use of a pharmaceutical composition comprising the polypeptide of SEQ ID No: 2 or 4, one of skill in the art cannot reasonable extrapolate the in vitro teaching or the gene therapy teachings of DIO-1 gene to the use of the polypeptides in vivo without undue experimentation.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 37-39, and 61are rejected under 35 U.S.C. 102(b) as being anticipated by Nagase *et al* (DNA Research 1997; 4(2):pages 141-150; cited on IDS filed 3/12/2001). Nagase *et al* teach the characterization of a cDNA clone that would inherently encode polypeptide variants of SEQ ID No: 1 and 3 (see attached sequence comparison). Because the specification does not specifically define the metes and bounds of a

"variant" and because this includes any type of variation from the actual sequences of SEQ ID Nos:1-4, the claims are anticipated.

Conclusion

14. Claim 40 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
May 18, 2004

GARY NICKOL
PRIMARY EXAMINER